Br Heart J 1991;66:206-11

Differences in first dose response to angiotensin converting enzyme inhibition in congestive heart failure: a placebo controlled study

R J MacFadyen, K R Lees, J L Reid

Abstract

***Objective*—To compare the first dose responses to low dose angiotensin converting enzyme inhibitors (captopril, enalapril, and perindopril) in elderly patients with stable chronic heart failure.**

***Design*—Double blind, randomised, placebo controlled, parallel, group prospective study of elderly patients with stable chronic heart failure.**

***Setting*—General hospital in-patient admissions for supervised diuretic withdrawal (24–48 hours) and the introduction of angiotensin converting enzyme inhibitor therapy.**

***Patients*—48 unselected elderly (58–85 years) patients with symptomatic but stable chronic heart failure (New York Heart Association grades II–IV) confirmed by clinical history, examination, and cardiological investigations. Patients gave their written and informed consent to receive their initial treatment under double blind conditions; blood pressure was monitored and blood samples taken to measure the pharmacokinetic and neurohormonal responses.**

***Intervention*—Patients were randomised to receive a daily oral dose of placebo, captopril (6·25 mg), enalapril (2·5 mg), or perindopril (2 mg).**

***Main outcome measures*—Blood pressure and heart rate responses, drug concentration, and plasma renin and ACE activities. Differences between treatment groups were analysed by analysis of variance.**

***Results*—The four randomised groups of patients had similar age, severity of heart failure (NYHA class), pretreatment diuretic dosage, plasma renin activity, and serum electrolyte state. Placebo treatment caused a modest but significant diurnal fall in blood pressure. Captopril produced a significant early (1·5 hours) and brief fall in blood pressure. The blood pressure fall with enalapril was later (4–10 hours), longer lasting, and was associated with significant slowing of supine heart rate. Though perindopril produced a similar plasma ACE inhibition to that produced by enalapril, it only caused changes in blood pressure that were similar to those caused by placebo.**

***Conclusions*—This controlled study is the first to indicate a qualitative difference in the acute response to angiotensin converting enzyme inhibitors with similar structure and metabolism (that is, enalapril and perindopril). Low dose perindopril seems to be less likely to cause hypotension in patients with heart failure. The explanation for the differences is unclear but may reflect differential effects on local tissue angiotensin generation.**

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Accepted for publication 25 March 1991

Several angiotensin converting enzyme (ACE) inhibitors have been shown to be valuable in the management of chronic heart failure.[1-4] They relieved symptoms, improved haemodynamic function, and reduced the associated mortality regardless of the aetiology of the syndrome. Efficacy has been well documented for moderate to severe chronic heart failure (New York Heart Association (NYHA) grades III–IV) and more recent studies suggest benefit in milder disease.[5] In most instances treatment with ACE inhibitors has been studied as an adjunct to diuretic and in some instances digoxin treatment. A series of case reports and small studies showed a considerable fall in blood pressure in response to the first dose of ACE inhibitor in patients with mild heart failure.[6] The origins of this response remain unclear. It may partly reflect activation of the circulating and tissue based renin angiotensin system either as a response to chronic heart failure[7] or to preceding or concurrent diuretic treatment.[8] It may be an expression of the range of individual sensitivity or responsiveness to the drug and dose used. Some workers have highlighted the role of reflex vagally mediated hypotension occurring in these patients via the Bezhold-Jarisch reflex.[9] In view of this background, clinicians have empirically used hospital admission for supervised treatment, dose reduction, variable periods of diuretic withdrawal, and blood pressure monitoring.[10]

Non-invasive, placebo controlled, comparative studies of the low doses currently used are rare. In addition, with the increasing range of ACE inhibitors the possibility of an agent specific element to this hypotensive response has not been adequately considered. We have conducted a randomised, double blind, parallel group study in elderly patients with stable chronic heart failure who were

routinely admitted to hospital for supervised diuretic withdrawal and initiation of treatment with ACE inhibitors. We compared the responses to low oral doses of three agents and placebo.

Patients and methods

A single dose randomised, double blind, placebo controlled, parallel group study was conducted in 48 unselected elderly (58–85 years) patients admitted to hospital for supervised initiation of treatment with an ACE inhibitor. We selected patients with chronic heart failure who were symptomatic on diuretic treatment (generally >80 mg frusemide or equivalent/day). None had an important fluid imbalance by clinical criteria nor an acute decompensation in the preceding three months. The diagnosis was confirmed by clinical history and by physical, radiological, and electrocardiographic examination before treatment. Many patients also underwent echocardiography or radionuclide scanning, or had been investigated by cardiac catheterisation. All patients had stable renal function and normal serum sodium (⩾135 mmol/l) before treatment.

Four study groups (n = 12) were given oral captopril 6·25 mg, oral enalapril 2·5 mg, oral perindopril 2 mg, or oral placebo (lactose) within an opaque gelatin capsule. Table 1 shows the characteristics of the four groups. The study protocol was approved by the local research and ethics review committee. All patients gave their written and informed consent to take part in the study.

PROCEDURE

Diuretic treatment was withdrawn for 24–48 hours before treatment and in most this was 48 hours. Concomitant treatment with vasoactive agents was stopped on the day of study and was not resumed until after non-invasive haemodynamic monitoring was complete 24 hours after dosing with ACE inhibitor or placebo. Digoxin, where prescribed, was continued unaltered. On the morning of the study (at about 07 30 hours) a heparinised peripheral venous cannula was inserted in an antecubital vein to take blood samples. Blood pressure was recorded (Sentron, Bard, Sunderland, UK) automatically every two minutes while the patients had a light breakfast and rested supine for at least 30 minutes before treatment. Baseline blood pressure was established over this period. After the period of rest venous blood was drawn for baseline determinations of plasma ACE and renin activities, routine biochemistry, haematology, and serum drug concentration. Oral treatments were administered double blind in their standard formulations within an opaque gelatin capsule prepared in accordance with the randomisation schedule held by the department of pharmacy.

After oral dosing blood pressure was measured in supine patients every 2 minutes with additional triplicate determinations at set time points. Blood samples were withdrawn frequently to determine the pharmacokinetic profile, ACE activity, and renin activity. Patients remained supine and received their normal meals throughout the study until 10 hours after dosing. Then they were allowed to rise but they were supine for at least 45 minutes before further blood sampling and blood pressure recordings at 24 hours after dosing. After this the nature of treatment was decoded and further treatment was arranged including re-instatement of diuretics and vasodilators at the discretion of the clinical staff. Patients receiving placebo continued on diuretic withdrawal and received open captopril with conventional observation on the ward. These patients were not included in any other active treatment group.

Table 1 Characteristics of patients

	Placebo (n=12)	*Captopril (n=12)*	*Enalapril (n=12)*	*Perindopril (n=12)*
M:F (n)	11:1	8:4	6:6	6:6
Age (mean (1 SD)) (yr)	68·2 (5·7)	67·8 (5·6)	65·9 (7·3)	69·2 (7·9)
NYHA class				
II	3	6	4	3
III	9	5	8	9
IV	—	1	—	—
Aetiology of CCF				
Ischaemic heart disease	6	7	6	4
Alcohol related cardiomyopathy	1	—	—	—
Dilated cardiomyopathy	1	—	3	3
Valvar heart disease	—	1	—	—
Combinations of above	4	4	3	5
Atrial fibrillation	2	2	—	3

CCF, chronic heart failure.

LABORATORY AND STATISTICAL ANALYSIS

We used high pressure liquid chromotography to measure the drug concentration and plasma ACE activity from the production of hippuric acid released from the exogenous substrate Hip-His-Leu.[11] Owing to the special sample preparation required with captopril to avert in vitro dimer formation and dissociation from ACE neither drug concentrations nor ACE activity could be assessed in the captopril group. Plasma renin activity was assessed by generation of angiotensin II from exogenous angiotensin I measured by radioimmunoassay.[12] The mean of triplicate mean arterial blood pressure (BP) (diastolic BP + ((systolic BP − diastolic BP)/3)) and heart rate recordings was used for statistical analysis both as absolute values and as changes from baseline. Repeated measures analysis of variance was applied, followed where appropriate by multiple t testing using Bonferroni correction for treatment effects at given time points. Effects with a p value $<0·05$ were regarded as significant. Data are shown as mean (1 SD). Biochemical indices were compared by one way ANOVA, and NYHA class was compared by Kruskal-Wallis ANOVA by ranks. Plasma renin activity was compared after logarithmic transformation.

Results

GENERAL

Each of the parallel groups contained patients of a similar age distribution, NYHA class, and

Table 2 Summary of comparisons for pre and post treatment laboratory data, age, and NYHA class

	Placebo	Captopril	Enalapril	Perindopril	ANOVA p=
Age	−68·2 (5·7)	67·8 (5·6)	65·9 (7·3)	69·2 (7·9)	0·677
Na^+	138·9 (2·5)	141·2 (3·4)	140·3 (2·7)	140·8 (2·4)	0·220
Δ Na^+	−0·2 (2·8)	+0·1 (2·3)	−0·5 (2·1)	+0·3 (1·2)	0·794
K^+	4·1 (0·6)	4·2 (0·3)	4·2 (0·6)	3·9 (0·6)	0·407
Δ K^+	+0·02 (0·6)	−0·15 (0·4)	+0·05 (0·6)	+0·08 (0·4)	0·684
Urea	8·5 (5·9)	6·3 (1·7)	7·2 (2·5)	8·6 (3·2)	0·380
Δ urea	−1·4 (4·0)	−0·1 (1·1)	−0·4 (1·3)	−0·4 (1·8)	0·570
Creatinine	107 (15)	98 (22)	102 (29)	122 (36)	0·150
Δ creatinine	−0·6 (19)	−4·0 (12)	−8·2 (16)	−6·6 (15)	0·651
Hb	14·4 (1·3)	13·5 (1·4)	14·0 (1·2)	13·8 (1·1)	0·408
Δ Hb	−1·2 (0·6)	−1·2 (0·5)	−1·8 (0·5)	−1·2 (0·5)	0·016
NYHA (average rank)	26·7	21·3	24·0	26·0	0·681*

*Kruskal-Wallis.

baseline laboratory variables. None of the laboratory indices was significantly altered by treatment in any of the parallel groups with the exception of a modest fall in haemoglobin which we have previously seen and attributed to blood sampling (table 2). No patient experienced important symptoms during diuretic withdrawal or the study period and all left hospital without ill effect after adjustment of diuretic dosage and of other drugs.

HAEMODYNAMIC FUNCTION

There were differences between the groups in the pretreatment baseline blood pressure and heart rate values. Baseline mean arterial pressure was significantly higher ($p < 0·05$) in the group treated with enalapril (106·4 (11·6) mm Hg) than in those who received captopril (98·4 (10·8)), perindopril (98·2 (11·0)), or placebo (100·3 (12·8)). In addition, the baseline supine heart rate was significantly lower ($p < 0·05$) in the group who were treated with captopril (75·9 (9·8) beats/minute) than in those who received enalapril (83·3 (15·9)), perindopril (77·1 (10·4)), or placebo (81·1 (12·8)). For these reasons the temporal pattern of response was described as the change from individual baseline pressures and heart rate rather than absolute values. This did not materially alter the general trends and the statistically significant differences.

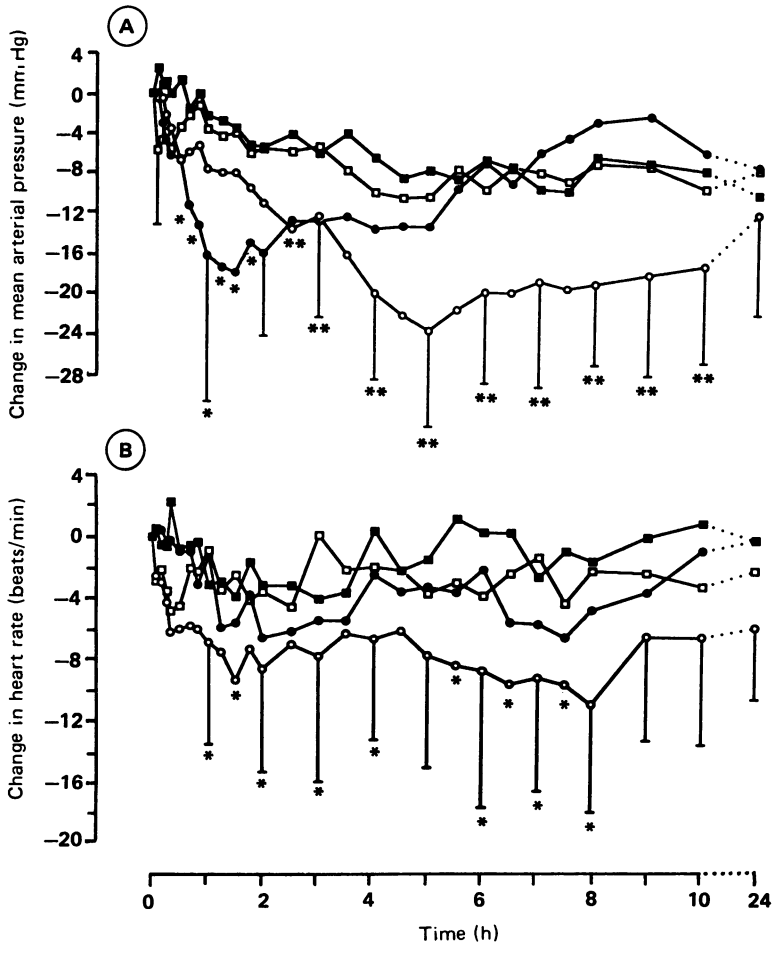

Figure 1 Baseline-corrected mean effect (1 SD) of oral placebo (□), captopril 6·25 mg (●), enalapril 2·5 mg (○), or perindopril 2 mg (■) on supine mean arterial pressure (A) and heart rate (B) in patients with chronic heart failure.

Mean arterial pressure fell during placebo treatment by approximately 10 mm Hg over the first 4·5 hours. Compared with the other treatments, captopril produced a significant fall in blood pressure (trough at 1·5 hours). Blood pressure had largely returned to normal by six hours. Enalapril produced a smooth and protracted fall in mean arterial pressure that was significantly greater than that produced by placebo from two to five hours (maximum at four to five hours post-dosing). Pressure remained significantly depressed at 10 hours. In contrast, after perindopril the mean arterial pressure did not significantly differ from placebo throughout the period of study (fig 1A). The individual maximum fall in mean arterial pressure from baseline was calculated. The mean maximum fall in the perindopril group (−15·1 (8·2), range −2 to −30·1 mm Hg) was similar to that seen with placebo (−16·4 (7·7), range −4 to −31·9 mm Hg). The mean maximum fall in mean arterial pressure for both the captopril (−22·4 (11·6), range −14 to −45·7) and enalapril (−26·4 (7·5), range −13·8 to −43) groups was significantly greater ($p = 0·012$).

Baseline corrected changes in mean supine heart rate were small in absolute terms. However, the group treated with enalapril showed a significant fall between one and eight hours after dosing (−10·8 (7·2) beats/minute) compared with placebo (−2·0 (9·6) beats/minute). This was not evident with captopril or perindopril (fig 1B).

ACE ACTIVITY AND RENIN AND DRUG CONCENTRATIONS

Pretreatment plasma renin activity (geometric mean, 95% confidence interval) after 24–48 hours of diuretic withdrawal was similar in all groups ($p = 0·183$, one way ANOVA); captopril group (1·1, 0·2 to 3·8 ng AI/ml/h) compared with placebo (3·2, 0·5 to 11·7), enalapril (1·7, 0·5 to 44·7), and perindopril (2·5, 0·2 to 11·9). There was no significant difference ($p = 0·222$ Kruskal-Wallis ANOVA) in the prestudy dose of diuretic drugs (mg frusemide/day) between those patients who received captopril (93 (33)), enalapril (85 (38)), perindopril (120 (40)), or placebo (110 (61)). All three active treatments increased plasma renin activity. The early rise associated with captopril was small because the initial sample was taken two hours after dosing. Enalapril and perindopril caused rises later (fig 2).

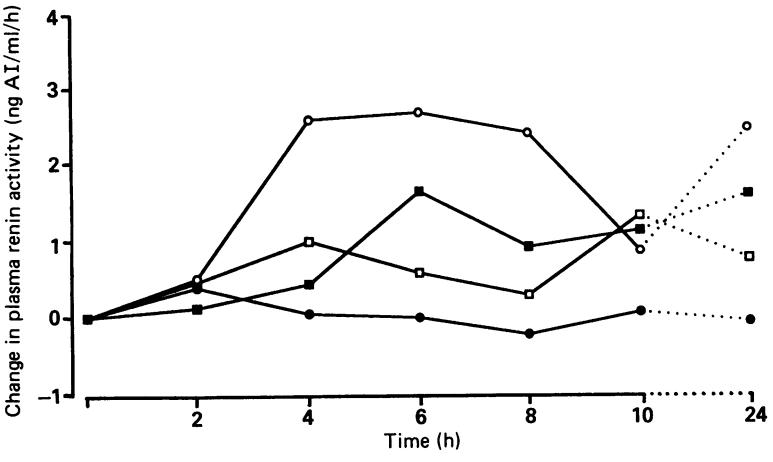

Figure 2 Plasma renin activity (geometric mean value) after oral placebo (□), captopril (●), enalapril (○), or perindopril (■).

Plasma ACE activity was significantly lower in both the perindopril and enalapril groups than in the placebo group (fig 3). Maximum ACE inhibition was similar in both active treatment groups (enalapril 63% and perindopril 68%) eight hours after dosing. The onset of inhibition was earlier with perindopril. Inhibition was significantly greater between 50 minutes and three hours after perindopril than after enalapril. After perindopril ACE inhibition was also significantly greater at 24 hours after dosing.

Figure 4 shows the pharmacokinetic profiles for the enalapril and perindopril groups. Concentrations of both the parent ester and active diacid metabolite were higher for enalapril than for perindopril. The mean (1 SD) time to peak ester concentrations (t_{max}) was 1·95 (0·7) hours for enalapril and 1·74 (0·7) hours for perindopril. The mean time to peak enalaprilat concentration was 6·9 (2·0) hours and that for perindoprilat was 5·48 (2·9) hours. In neither instance was there a significant difference between the groups in t_{max} for either ester ($p = 0·684$) or diacid ($p = 0·229$) (Kruskal-Wallis ANOVA). Generally speaking both treatments were associated with prolonged plateau concentrations of the active diacid.

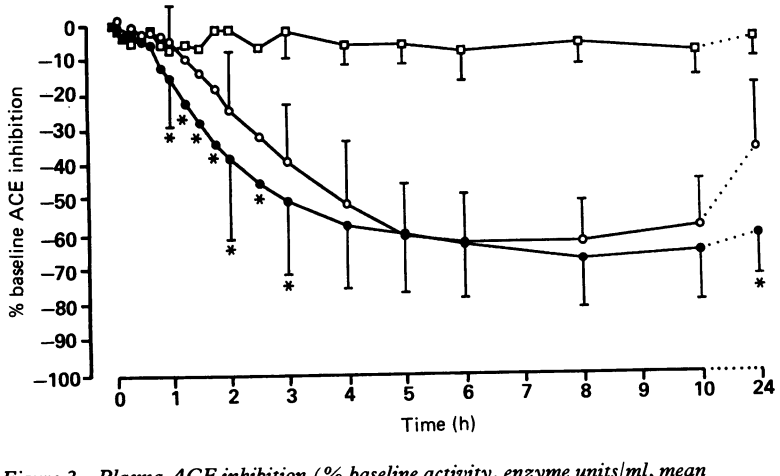

Figure 3 Plasma ACE inhibition (% baseline activity, enzyme units/ml, mean (1 SD)) after placebo (□), enalapril (○), or perindopril (●).

Discussion

We found significant differences in the responses to the recommended low doses of ACE inhibitors in elderly patients with chronic heart failure during temporary diuretic withdrawal. The use of a placebo controlled, randomised, parallel group design in this study allowed us to compare drug effects. To control for diurnal changes and feeding patterns,[13] it is important to compare the haemodynamic responses in these patients with those of a placebo treated group. We chose a parallel group design to avoid a carryover effect caused by the protracted elimination phase associated with some ACE inhibitors[14] and to avoid delay in the initiation of active treatment.

The first dose hypotensive response to ACE inhibitors in chronic heart failure has received much attention in case reports and small series. It has been reported to be associated with transient renal hypoperfusion damage.[15] However, the mechanism and significance of the response in clinical practice remain obscure. The relation of blood pressure fall to previous or concurrent diuretic therapy, the dose or type of ACE inhibitor used, and the importance of the range of individual patient responses are poorly defined. We chose to compare the degree and pattern of blood pressure response in the group of patients that we considered to be at greatest risk of developing a hypotensive response—elderly, diuretic treated patients with moderate to severe heart failure.

Though we used the standard low doses of both captopril and enalapril both these drugs caused falls in blood pressure consistent with previous reports. If, as some workers suggest, the first dose blood pressure response is related to the prevailing activation of the renin angiotensin system, as predicted by circulating renin activity,[16] it might be that our observations are an underestimate of the general degree of response in the captopril treated group. Nevertheless, we documented predictable and significant supine blood pressure falls regardless of diuretic withdrawal and relatively (but not significantly) lower renin activity in this group. Experience with lower oral doses of captopril—for example, 1 mg[17]—is limited, but their formulation is compromised by chemical instability.[18] Patterns of test dosing with captopril have been suggested but the individual relevance of this strategy to subsequent responses to higher doses of the same or different agents has not been documented. Captopril is frequently selected on the empirical basis that if symptomatic hypotension and hypoperfusion were to occur their duration would at least be limited compared with longer acting drugs.[19] Our comparison between low dose captopril and enalapril confirms this pattern. We found that neither captopril nor enalapril caused symptoms or adverse changes in renal biochemistry.

In contrast, low dose perindopril was not associated with any change in blood pressure or heart rate, though it caused comparable plasma ACE inhibition which, if anything, was more prolonged than after enalapril. This may

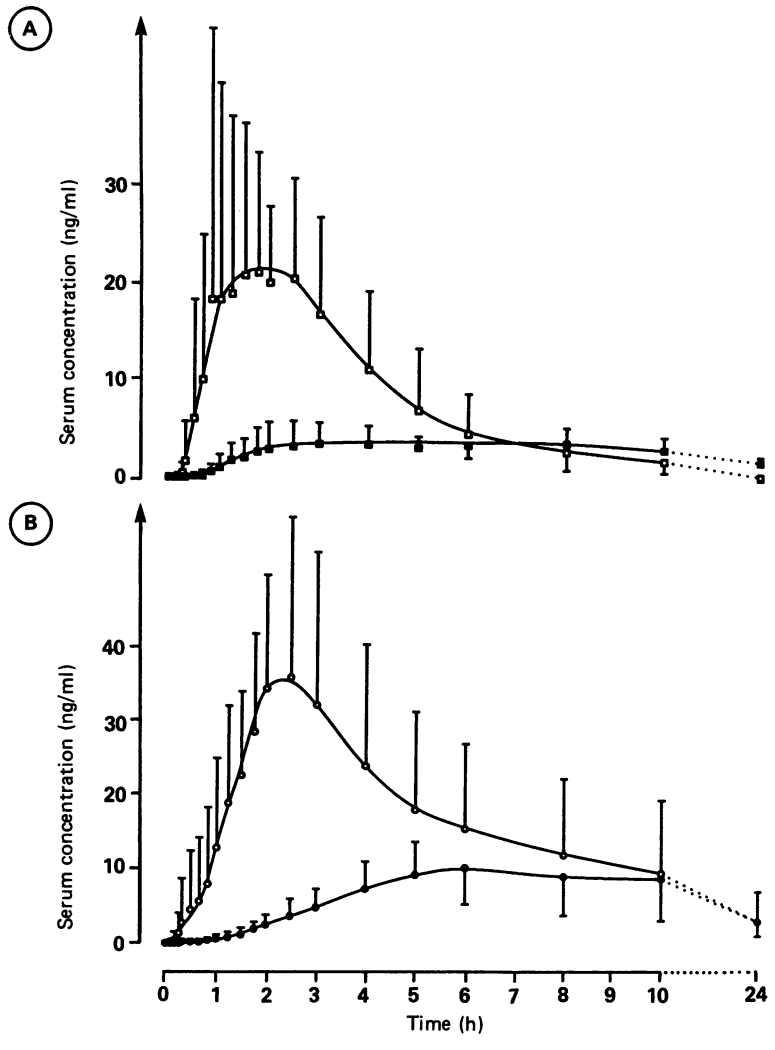

Figure 4 Mean serum concentrations (1 SD) of perindopril (□), and perindoprilat (■) (A) or enalapril (○) and enalaprilat (●) (B) after oral treatment in patients with chronic heart failure.

therefore reflect an important and clinically relevant agent-specific difference in response between ACE inhibitors. The comparison was performed in patients who remained supine in a controlled hospital setting. The ambulatory blood pressure response would be expected to follow a similar pattern. At the doses selected there was a similar differential response in heart rate. Altered autonomic tone and baroreceptor reflexes in patients in heart failure are well known[20] as are the antiadrenergic or parasympathomimetic properties of captopril,[21] enalapril,[22] and perindopril.[23] To our knowledge this is the first demonstration of a small but significant slowing of basal heart rate in a study of supine patients after low dose enalapril with an appropriate placebo control group. This effect on heart rate was seen only briefly with captopril and not seen at all with perindopril.

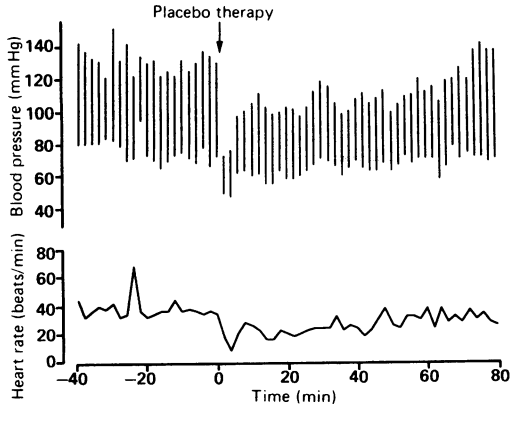

Figure 5 Individual blood pressure and heart rate profile of patient (case 27) on double blind placebo therapy.

One of the proposed mechanisms for the fall in blood pressure in a proportion of heart failure patients treated with ACE inhibitors is activation of the Bezhold-Jarisch reflex by vagally mediated hypotension and bradycardia.[24] One of our patients had a considerable fall in blood pressure and associated bradycardia yet remained symptom free immediately after dosing with placebo (fig 5). He subsequently tolerated open captopril therapy on the following day without complications. His placebo response was not excluded from our analysis. This reflex mechanism may be relevant in a few reported cases of hypotension after ACE inhibitors in heart failure patients. The Bezhold-Jarisch reflex clearly has little relevance to specific ACE inhibitors, agent selection, or general management policies designed to avoid hypotension in heart failure because it is unpredictable and not related to dose or to individual drugs.

Studies with ACE inhibitors over the past 5–10 years have generated interest in the role of tissue based angiotensin generating systems with local autocrine or paracrine roles.[25] There is indirect evidence for such local systems in many tissues including heart, kidney, adrenal, brain, and blood vessels. Recent studies in animals with experimental heart failure suggest an activation of the tissue based angiotensin generating system.[26] However, there is as yet no direct evidence of the clinical significance of any tissue based renin angiotensin system to responses to ACE inhibitor drugs in man. In this acute study we found similar plasma ACE inhibition with both enalapril and perindopril yet the blood pressure responses were different. Differences in penetration and interaction with the tissue renin angiotensin systems may explain this finding. With both these drugs the net interaction with tissue and plasma ACE will be a product of the parent ester, a weak but lipid soluble ACE inhibitor, and the more potent but polar diacid metabolite. The potency ratios and polarity of ester and diacid vary substantially between different compounds despite a similar basic structure and there is limited in vitro evidence that the interaction is significant at least for plasma ACE.[27] At different tissue sites the bioavailability of each of these components would also be expected to vary and contribute further to potential differences in the pattern of tissue ACE inhibition. Because long term treatment involves the attainment of an equilibrium the most likely setting in which potential differences would be apparent is the first dose response.[28]

The interpretation of plasma ACE inhibition after chronic dosing with ACE inhibitor drugs is complicated by the coexistent reactive rise in renin activity. Moreover, substrate analysis of ACE activity may not give an absolute indication of circulating angiotensin peptide con-

centrations after chronic administration of different ACE inhibitors.[29] These factors are unlikely to be relevant to the acute responses described in heart failure patients in this study. In addition, they would not adequately explain the qualitative difference in blood pressure response between enalapril and perindopril.

Angiotensin converting enzyme is well known to be a non-specific metalloprotease and its inhibition has important interactions potentiating vasodilatatory prostaglandins and inhibiting the degradation of bradykinin. It is as yet unclear what these general interactions contribute to the cardiovascular effects of ACE inhibitors.[30] We are unaware of any experimental or clinical studies indicating the relevance of these interactions to the response to ACE inhibitors in heart failure. We think that the differential blood pressure responses observed are unlikely to be explained through differences in kinin or prostaglandin metabolism.

The significance of acute haemodynamic responses to ACE inhibitor drugs in patients with chronic heart failure is unclear. Pronounced responses are not markers of symptomatic benefit and, conversely, smaller blood pressure falls can be associated with benefit.[31] In general terms improvements in exercise duration and symptoms seem to require six to eight weeks of therapy and alternative mechanisms may be important in reducing mortality.[32] Because perindopril has been shown to provide symptomatic improvement in chronic heart failure,[4] similar to other ACE inhibitors, the lack of an initial blood pressure fall does not seem to be an indication of a lack of long term efficacy in heart failure. However, in acute heart failure perindopril may not share the haemodynamic benefits that have been shown with other ACE inhibitors.[33]

Our results indicate that clinically significant differences in responses to ACE inhibitor drugs can be observed in patients with chronic heart failure in a controlled hospital setting. Our study has general relevance because the patient population was not highly selected and because it included primarily the "high risk" groups of the elderly, diuretic pretreated patients with severe chronic heart failure. Any manoeuvre that reduces the risk of hypotensive responses in these patients may have clinical and possibly resource implications. The patient population, dose and agent used, and the adequate definition of haemodynamic and biochemical responses are important. Further study is required to define the explanation of the differences between the ACE inhibitors seen in our study.

We thank Dr F G Dunn, Dr W S Hillis (Stobhill Hospital), and Dr J A Kennedy (Western Infirmary, Glasgow) for allowing us to study their patients, Servier Laboratories (Slough, UK) for supplies of low dose perindopril, Mr G M Thomson and Ms L M Gilbert (Department of Pharmacy, Stobhill Hospital) for randomisation and preparation of treatments, and Mr J McCulloch and Mr D M Hughes for technical assistance. This study was supported by the British Heart Foundation.

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